Quantification of noise in the bi-functionality induced post-translational modification

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We present a generic analytical scheme for the quantification of fluctuations due to bi-functionality induced signal transduction within the members of bacterial two-component system. The proposed model takes into account post-translational modifications in terms of elementary phosphotransfer kinetics. Sources of fluctuations due to autophosphorylation, kinase and phosphatase activity of the sensor kinase have been considered in the model via Langevin equations, which are then solved exactly within the framework of linear noise approximation. The resultant analytical expression of phosphorylated response regulators are then used to quantify the noise profile of biologically motivated single and branched pathways. Enhancement and reduction of noise in terms of extra phosphate outflux and influx, respectively, have been analyzed for the branched system.

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I. INTRODUCTION

The response of living systems in presence of an external stimulus is coordinated by highly specialized signal transduction machinery. In the bacterial kingdom this is achieved by the well characterized two-component system (TCS) minimally comprised of the membrane bound sensor kinase (SK) and the cytoplasmic response regulator (RR) [1–3]. The machinery of TCS is utilized by the bacteria to process the information of external signals in terms of phosphotransfer kinetics. When applied, an external stimulus causes phosphorylation at the histidine residue of SK which then gets transferred to the cognate (and/or non-cognate) RR at their aspartate domain. The phosphorylated RR then acts as a transcription factor for several downstream genes, as well as for the activation/represion of its own operon. It is now a well established fact that in addition to being a source (kinase), a SK can equally act as a sink (phosphatase) while interacting with a RR. Such bi-functional behavior of a SK towards RR can altogether build a robust motif in the bacterial signal transduction network [4–7].

Expression of proteins in individual cell is usually driven by the fluctuations present within the cellular environment as well as the fluctuations imposed by the external stimulus [8–14]. This often leads to variability in the expression level within the context of single cell [15–18]. When observed in the bulk such fluctuations gets averaged out over the cellular population. The prevalent fluctuations, whether external or internal, do not only effect the dynamics of gene expression it plays a major role in post-translational modification as well [19, 20]. In this connection it is also important to mention the role of cellular fluctuations in the different signal transduction motif that primarily uses phosphotransfer mechanism. Using a push-pull amplifier loop mechanism theoretical study has been made to analyze the signal transduction within the photoreceptor of retina [21]. Theoretical model has been proposed to study the effect of reversibility in the phosphorylation-dephosphorylation cycle that can generate bistable behavior in the presence of noise and can propagate within the signaling cascade [22]. In the context of robustness in bacterial chemotaxis, reversibility on a signaling cascade has been shown to exert a stabilizing effect of adaptation through methylation [23]. Correlation between extrinsic and intrinsic noise that arises due to external signal and internal biochemical pathways, respectively, has been reported to enhance the robustness of zero-order ultrasensitivity [24].

Post-translational modification in terms of phosphate transfer is important to generate the pool of phosphorylated RR that act as a transcription factor for several downstream genes. Bi-functionality on the other hand plays a crucial role to maintain this pool as the information flows through the phosphotransfer motif. Thus bi-functionality and post-translational modification works hand in hand to maintain the optimal pool of phosphorylated RR. Since this composite functional behavior take place in a noisy cellular environment it is worthwhile to investigate the role of cellular noise on the bi-functionality controlled post-translational modification of the components of the well composed signal transduction machinery. The specific question we aim to address here is how the cellular fluctuations affect this functional motif or in a noisy environment whether individual cell can maintain bi-functionality while generating optimal level of noise? To address this questions we develop in the present communication a generic mathematical model to study the role of molecular noise on the post-translational modification of system components and on

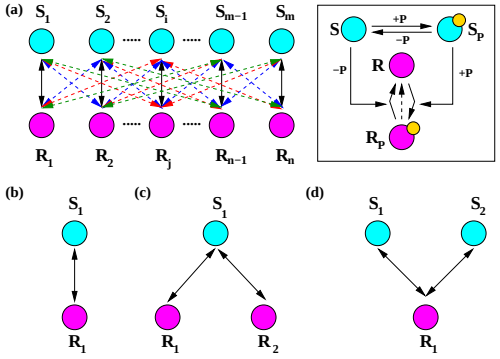

FIG. 1. (color online) The wiring diagrams for the proposed post-translational interactions between SK and RR. The cyan and magenta blob stands for the SK and RR, respectively. (a) The generalized m:n system with cognate (solid black arrow) and non-cognate (dashed colored arrow) kinase and phosphatase interactions. (b), (c) and (d) are wiring diagram for 1:1, 1:2 and 2:1 interactions, respectively. The boxed wiring diagram depicts the phosphate addition (+P) and removal (-P) kinetics between a pair of cognate and/or non-cognate SK and RR that ultimately results into phosphorylated RR (magenta blob with a yellow blob on top). The dotted arrowhead is for auto-dephosphorylation of RR. For simplicity we do not show the yellow blob in (a)-(d).

the bi-functionality of the signal transduction machinery of bacterial TCS.

II. THE MODEL

We start by considering a simple system describing post-translational modification due to phosphotransfer mechanism of a typical TCS, where m numbers of SK interacts with n numbers of RR, the ultimate product of which is R_p, the phosphorylated RR. We call the proposed model as the m:n system (Fig. 1a) where each of the SK, RR and their phosphorylated forms are designated as S, R, S_p and R_p, respectively. The generic model we consider here involves single pair interaction (Fig. 1b). In addition it takes care of *branched pathways* [3]; for example the 1:2 system (Fig. 1c) mimics the *one to many* pathway as observed in chemotaxis system in *E. coli*, where the SK CheA phosphorylates two RR, CheY and CheB [25]. Similarly the 2:1 system (Fig. 1d) follows the kinetics of *many to one* pathway as observed in *V. cholerae* where the SK LuxS and CqsS phosphorylate the RR LuxO [26], respectively.

As mentioned earlier, in typical bacterial TCS the key steps of phosphotransfer mechanism involve autophosphorylation at SK, transfer of phosphate group from SK to RR, and SK mediated removal of phosphate group from RR (see boxed diagram in Fig. 1). To keep the model simple we do not consider the synthesis (birth) or degradation (death) of any system component. The interaction we consider here may be of cognate and/or non-cognate type. Out of the m:n pair one can consider the specific interaction between i-th SK and j-th RR, where $1 \leqslant i \leqslant m$ and $1 \leqslant j \leqslant n$, to write down the elementary kinetic steps considering the minimal interaction between a specific pair

$$S_i \underset{k_{-i}}{\overset{k_i}{\rightleftharpoons}} S_{pi}, \tag{1a}$$

$$S_{pi} + R_j \xrightarrow{k_{kij}} S_i + R_{pj}, \tag{1b}$$

$$S_i + R_{pj} \xrightarrow{k_{pij}} S_i + R_j. \tag{1c}$$

$$R_{pj} \xrightarrow{k_{apj}} R_j. \tag{1d}$$

In the above kinetic steps, Eq. (1a) considers autophosphorylation at the histidine residue of the SK. Generally, autophosphorylation takes place under the influence of an external signal [1–3] which we consider to be of constant type and have been absorbed in the rate constant k_i. Eqs. (1b-1c) takes into account the kinase and phosphatase activity of the SK, respectively, thus considering the bi-functional behavior of the SK. Eq. (1d) denotes the auto-dephosphorylation of the RR independent of the phosphatase effect of SK on RR [6].

Due to the inherent noisy nature of the cellular environment each of the four reactions mentioned above are influenced by fluctuations and in turn affect the copy numbers of each system component. To take this into account we introduce Langevin noise terms that can influence each of the reactions independently given by Eqs. (1a-1d). The interaction of a single SK with multiple RR or *vice versa* in presence of fluctuations we consider here can be compared with stochastic system-reservoir formalism where a single system interacts with multiple reservoir or *vice versa* [27]. In terms of phosphate transfer, SK pumps in energy to RR when act as kinase, whereas the same withdraws energy from RR while acting as phosphatase. The stochastic differential equations describing the phosphorylated SK and RR in presence of fluctuations can be written as

$$\frac{dS_{pi}}{dt} = k_i(S_{Ti} - S_{Pi}) - k_{-i}S_{pi} - \sum_{j=1}^{n} k_{kij}S_{pi} \times(R_{Tj} - R_{pj}) + \xi_i(t) \tag{2a}$$

$$\frac{dR_{pj}}{dt} = \sum_{i=1}^{m} k_{kij}S_{pi}(R_{Tj} - R_{pj}) - \sum_{i=1}^{m}[k_{pij} \times(S_{Ti} - S_{Pi}) + k_{apj}]R_{pj} + \psi_j(t). \tag{2b}$$

Here $S_{Ti} = S_i + S_{pi}$ and $R_{Tj} = R_j + R_{pj}$ stand for the total amount of i-th SK and j-th RR, respectively. The noise terms ξ_i and ψ_j take care of the fluctuations in the copy number of S_{pi} and R_{pj}, respectively. Within the framework of linear noise approximation we define the statistical properties of the Langevin terms obeying the fluctuation-dissipation relation [20, 28–30] with zero

mean, $\langle \xi_i(t) \rangle = \langle \psi_j(t) \rangle = 0$ and

$$\langle \xi_i(t)\xi_i(t+\tau) \rangle = 2k_i(S_{Ti} - S_{Pi})\delta(\tau),$$
$$\langle \psi_j(t)\psi_j(t+\tau) \rangle = 2\sum_{i=1}^{m} k_{kij} S_{pi}(R_{Tj} - R_{pj})\delta(\tau),$$

with $\langle S_{pi} \rangle$ and $\langle R_{pj} \rangle$ being the mean values at the steady state. In addition, we consider both the noise terms are correlated [24, 31]

$$\langle \xi_i(t)\psi_j(t+\tau) \rangle = -k_{kij} S_{pi}(R_{Tj} - R_{pj})\delta(\tau).$$

Linearizing Eqs. (2a-2b) around the steady state, i.e., $S_{pi} = \langle S_{pi} \rangle + \delta S_{pi}$ and $R_{pj} = \langle R_{pj} \rangle + \delta R_{pj}$, we have

$$\frac{d}{dt}\begin{pmatrix} \delta S_{pi} \\ \delta R_{pj} \end{pmatrix} = \begin{pmatrix} -a_i & \sum_{j=1}^{n} k_{kij}\langle S_{pi} \rangle \\ \sum_{i=1}^{m} b_{ij} & -c_j \end{pmatrix} \times \begin{pmatrix} \delta S_{pi} \\ \delta R_{pj} \end{pmatrix} + \begin{pmatrix} \xi_i \\ \psi_j \end{pmatrix}, \quad (3)$$

where

$$a_i = \frac{k_i S_{Ti}}{\langle S_{pi} \rangle}, b_{ij} = (k_{pij} S_{Ti} + k_{apj})\frac{\langle R_{pj} \rangle}{\langle S_{pi} \rangle},$$
$$c_j = \sum_{i=1}^{m} \frac{[k_{pij}(S_{Ti} - \langle S_{pi} \rangle) + k_{apj}]R_{Tj}}{R_{Tj} - \langle R_{pj} \rangle}.$$

Solving Eq. (3) and performing Fourier transformation $\delta\tilde{X}(\omega) = \int_{-\infty}^{\infty} \delta X(t) e^{-i\omega t} dt$ on the resultant solution we have in matrix notation the generalized solution for both $\delta\tilde{S}_p(\omega)$ and $\delta\tilde{R}_p(\omega)$,

$$\boldsymbol{\delta\tilde{S}_p}(\omega) = \mathbf{A}^{-1}\left(\langle \mathbf{S_{pK}} \rangle \boldsymbol{\delta\tilde{R}_p}(\omega) + \boldsymbol{\tilde{\xi}}(\omega)\right), \quad (4a)$$

$$\boldsymbol{\delta\tilde{R}_p}(\omega) = \mathbf{P^{-1}}\left(\mathbf{B}^{\mathrm{T}}\mathbf{A}^{-1}\boldsymbol{\tilde{\xi}}(\omega) + \boldsymbol{\tilde{\psi}}(\omega)\right), \quad (4b)$$

where $\mathbf{P} = \mathbf{C} - \mathbf{B}^{\mathrm{T}}\mathbf{A}^{-1}\langle \mathbf{S_{pK}} \rangle$. In the above expressions (4a-4b), $\boldsymbol{\delta\tilde{S}_p}$ and $\boldsymbol{\delta\tilde{R}_p}$ are $m\times 1$ and $n\times 1$ dimensional column vectors with elements $\delta\tilde{S}_{pi}$ and $\delta\tilde{R}_{pj}$, respectively. Likewise, $\boldsymbol{\tilde{\xi}}$ and $\boldsymbol{\tilde{\psi}}$ are $m \times 1$ and $n \times 1$ column vectors with elements $\tilde{\xi}_i$ and $\tilde{\psi}_j$, respectively. $\mathbf{A}$ and $\mathbf{C}$ are diagonal matrix of order $m \times m$ and $n \times n$ with elements $(i\omega + a_i)$ and $(i\omega + c_j)$, respectively. Additionally, $\langle \mathbf{S_{pK}} \rangle$ and $\mathbf{B}$ are matrix of order $m \times n$ with elements $\langle S_{pi} \rangle k_{kij}$ and b_{ij}, respectively.

Since we are interested in the effect of noise on phosphorylated RR, R_p, which acts as transcription factor for one or more genes including the gene that encodes SK and RR we now focus on the solution of Eq. (4b) only. From the structure of Eq. (4b) it is clear that dynamics of R_p is now decoupled from S_p. To understand the role of fluctuations in phosphotransfer processes, we define the quantity noise at steady state, $\eta_{R_P} = \sigma_{R_p}/\langle R_p \rangle$. While calculating the noise for the three different systems (1:1, 1:2 and 2:1) mentioned in Fig. (1) we only focus on the noise level of R_{p1}, the phosphorylated form of R_1. Noise generated due to other interactions (S_1 and R_2, and S_2 and R_1) are considered to add extra layers of information

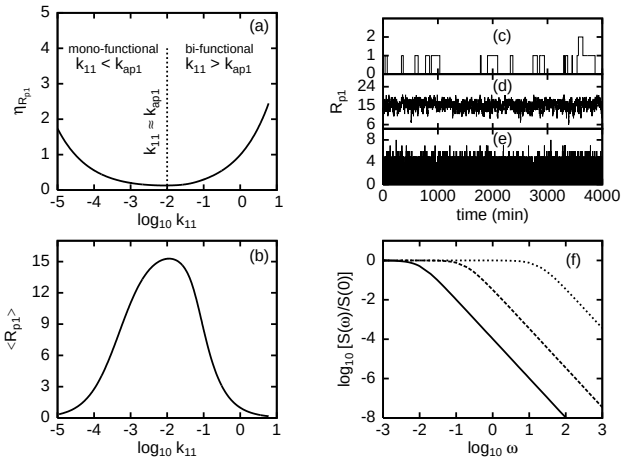

FIG. 2. Plot of noise, steady state protein level, time series and power spectra for 1:1 system. (a) Noise $\eta_{R_{p1}}$ as a function of $\log_{10} k_{11}$. The noise profile has been shown to contain three different regions, *viz* mono-functional region ($k_{11} < k_{ap1}$), crossover region ($k_{11} \approx k_{ap1}$) and bi-functional region ($k_{11} > k_{ap1}$). In the absence of auto-dephosphorylation kinetics (Eq. (1d)) only the bi-functional domain exists, whereas in the absence of phosphatase kinetics (Eq. (1c)) only the mono-functional domain becomes prevalent. (b) Steady state R_{p1} as a function of $\log_{10} k_{11}$. (c)-(e) Time series of R_{p1} for low ($k_{11} = 10^{-5}$), intermediate ($k_{11} = 10^{-2}$) and high ($k_{11} = 1$) values of k_{11}, respectively, generated using Gillespie algorithm [32, 33] (f) Normalized power spectra for low (solid line), intermediate (dashed line) and high (dotted line) values of k_{11}. In all the cases $k_1/k_{-1} = 5$, $k_{ap1} = 0.01$ and $S_{T1} = R_{T1} = 20$.

on the noise profile of R_{p1}. During the calculation of noise and power spectra we have considered $k_{kij} = k_{pij} = k_{ij}$ $(i, j = 1, 2)$, as kinase and phosphatase activity between SK and RR takes place via protein-protein interaction. It is important to note that while interacting with its partner a SK shows both mono-functional and bi-functional behavior for $k_{apj} > k_{ij}$ and $k_{apj} < k_{ij}$, respectively [6]. At $k_{apj} \approx k_{ij}$ (cross over regime) system makes transition from mono- to bi-functional domain.

III. RESULTS AND DISCUSSION

In Fig. (2a) noise profile of R_{p1} has been shown in a semilog plot. For 1:1 system at a low value of k_{11} noise has a nonzero value which goes down as k_{11} value increases. As k_{11} value increases further noise increases and reaches a higher value. As evident from the definition, noise is inversely proportional to the population of steady state R_{p1}. To check the role of $\langle R_{p1} \rangle$ on steady state noise we have calculated $\langle R_{p1} \rangle$ as a function of $\log_{10} k_{11}$ (Fig. 2b) from which it is clear that the protein profile develops exactly in the opposite way of the noise profile and imparts a inverse effect on the noise development.

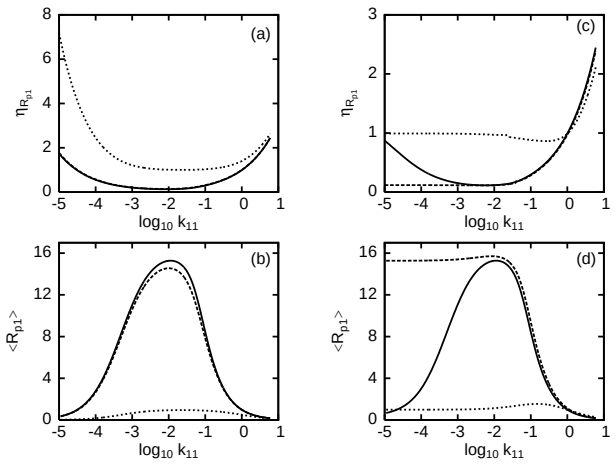

FIG. 3. Plot of noise and steady state protein level for branched (1:2 and 2:1) pathways. (a,c) Noise profile for 1:2 and 2:1 system, respectively, as a function of $\log_{10} k_{11}$. The solid, dashed and dotted lines are for low (10^{-5}), intermediate (10^{-2}) and high (1) values of k_{12} (for 1:2) and k_{21} (for 2:1). (b,d) Steady state level of R_{p1} for the same values of k_{12} and k_{21} as in (a,c). For all the cases $k_i/k_{-i} = 5$, $k_{apj} = 0.01$ and $S_{Ti} = R_{Tj} = 20$.

For the low value of k_{11} the auto-dephosphorylation k_{ap1} dominates over the phosphatase activity of SK on RR ($k_{11} < k_{ap1}$). In this regime the sensor shows mono-functional activity by acting as a kinase only, which is still lower than k_{ap1}. This effectively reduces the R_{p1} level (Fig. 2c) and increases the noise of the system. In the limit $k_{11} \approx k_{ap1}$ (vertical dotted line in Fig. 2a) R_{p1} level reaches at its maximum (Fig. 2b and Fig. 2d) while reducing the noise. When k_{11} exceeds k_{ap1} ($k_{11} > k_{ap1}$), the phosphatase activity of SK starts to show up in addition to its kinase activity. In this regime bi-functional property of SK comes into play reducing the copy of R_{p1} (Fig. 2e) henceforth increasing the noise of the system. To understand how the system relaxes under the influence of the protein protein interaction, we calculate the power spectra $S(\omega) = \langle \delta\tilde{R}_{p1}(\omega)\delta\tilde{R}_{p1}(\omega') \rangle$ (Fig. 2f). The resultant spectral lines are plotted for low, intermediate and high k_{11} ($= k_{k11} = k_{p11}$) values. As expected the power spectra relaxes faster for low k_{11} value compared to intermediate k_{11} value which again relaxes faster compared to higher k_{11} value. For a low value of k_{11} the conversion of R into R_p is a slow process and hence fast fluctuations in the copy number have minimal effect on the power spectrum. As k_{11} value increases the conversion rate increases and thus gets affected by the noise in the copy number which results into slower relaxation.

In Figs. (3a-3c) in a semilog plot we show the noise, $\eta_{R_{p1}}$ for 1:2 and 2:1 system as a function of k_{11}. For comparison we refer to noise profile of 1:1 system shown in Fig. (2a). In 1:2 system a single SK, S_1 interacts with two RR, R_1 and R_2, with its bifunctional properties acting on both the RRs. In Fig. (3a) we show the noise generated for R_{p1} while taking into account the kinase and phosphatase rates ($k_{k12} = k_{p12} = k_{12}$) between S_1 and R_2 to be low ($k_{12} = 10^{-5}$), intermediate ($k_{12} = 10^{-2}$) and high ($k_{12} = 1$). For low and intermediate k_{12} value the noise profile looks almost like 1:1 system as k_{11} is varied. This happens as interaction between S_1 and R_2 adds a weak layer of information on R_1 due to mono-functional property of S_1 on R_2 ($k_{ap2} \geqslant k_{12}$). Whereas for high k_{12} value a huge amplification of noise occurs (the dotted line in Fig. (3a)). In this domain as $k_{ap2} < k_{12}$, SK starts to show its bi-functional property and is more active in its interaction with R_2, rather than with R_1. Such active interaction between S_1 and R_2 adds an extra layer of outflux of phosphate group from R_1 (the dotted line in Fig. 3b) thus leading to low level of $\langle R_{p1} \rangle$ and enhancement of noise.

In 2:1 system a single RR, R_1 interacts with two SK, S_1 and S_2. In Fig. (3c) we show the noise generated for R_{p1} while taking into account the kinase and phosphatase rates ($k_{k21} = k_{p21} = k_{21}$) between S_2 and R_1 to be low ($k_{21} = 10^{-5}$), intermediate ($k_{21} = 10^{-2}$) and high ($k_{21} = 1$). For low value of k_{21} the noise profile is similar to that one for 1:1 system as k_{11} is increased. Although in this domain S_2 acts as kinase only, it provides a low level of input on R_1 as $k_{ap1} > k_{21}$. Interesting behavior emerges as k_{21} takes intermediate and high value. In the intermediate domain maximal level of $\langle R_{p1} \rangle$ is produced due to extra influx of phosphate group. This large influx due to k_{21} can overpower the low kinase effect of k_{11}, henceforth increases the steady state level of R_{p1} as a effect of which the noise level attains a minimum value. For high k_{21}, $k_{ap1} < k_{21}$ where S_2 starts to show its bi-functional property via phosphate input and removal. This helps the composite system to maintain a high value of noise for a wide range. Note that, compared to the low and intermediate domain the protein level in this region goes down drastically due to strong phosphatase activity of S_2 on R_1. It is interesting to note that for intermediate and high k_{21} value the composite system looses it mono-functional behavior almost completely (Fig. 3d).

IV. CONCLUSION

To conclude, we have provided a generic description for the calculation of noise due to post-translational modification in bacterial TCS. From exact analytical calculation within the purview of linear noise approximation it is possible to quantify the steady state noise for a single pair and branched pathways. For single pair system our analysis shows the effect of bi-functionality of SK on noise generation and could differentiate the mono- and bi-functional domain in the noise profile. Calculation for branched pathways shows enhancement and reduction of noise for the composite system in terms of extra phosphate outflux and influx, respectively. Our analysis sug-

gests that in *one to many* system as in the chemotaxis pathway of *E. coli* enhancement of fluctuations happens due to extra outflux of phosphate group within the members of TCS. On the other case, for *many to one* system mimicking the quorum sensing network of *V. cholerae* an optimal level of noise can be maintained via extra influx of phosphate group. To maintain such low noise activity SK of *V. cholerae* phosphotransfer circuit might prefer to operate in the cross over domain.

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